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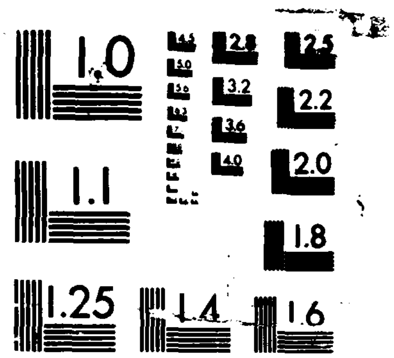


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L-TRYPTOPHAN, SLEEP, AND PERFORMANCE

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## SUMMARY

Planning for adequate rest and predicting the consequences of inadequate sleep or cumulative sleep loss should be an important consideration in mission logistics. The use of a sleeping aid may be appropriate to permit personnel to maximize sleep effectiveness in operational environments. At NHRC, we have investigated the amino acid l-tryptophan as a "nonsedating" sleeping aid for military use. Attention focused on l-tryptophan because of its role as the dietary precursor of serotonin, the neurotransmitter first identified by Jouvet as involved in the regulation of sleep. Recent reviews continue to debate the effectiveness of l-tryptophan as a sleeping aid and the underlying mechanism for its effects.

At the present time, there seems to be general agreement that l-tryptophan, administered at the right time and in adequate doses, does promote increased sleepiness in awake subjects and more rapid daytime and nighttime sleep onset. In our program in Behavioral Psychopharmacology, we have conducted 3 studies on the efficacy of l-tryptophan using different subject types and requiring sleep at different times of day or in different environments. In a daytime nap study, normal sleepers were required to take daytime naps at 0950 or 1350, once after l-tryptophan 4 g and once after placebo. L-tryptophan significantly reduced sleep latency in both morning and afternoon naps. In a study of 6 consecutive nights of use of l-tryptophan 3 g, young (age 20.3 $\pm$ 2.4 years), chronic sleep-onset insomniacs showed more rapid sleep onset late in administration, but not on the first 3 nights of use. These and other studies suggest that normal sleepers may respond to l-tryptophan administration on the first occasion of use, while more chronic insomniacs may require "pretreatment" before sleep-enhancing effects are evident. More recently, in a study of Marines airlifted to Okinawa, l-tryptophan 2 g was administered en route aboard the aircraft and 1 h before bedtime for 3 nights after arrival. Objective sleep data were obtained using Medilog recorders. Total nocturnal sleep was increased by 52 minutes on the first night after arrival. This finding suggests that l-tryptophan is adequately effective to be used in the field to alleviate jet lag. We also evaluated the effects of l-tryptophan on performance, memory, and arousal threshold during sleep using a standard laboratory protocol. Unlike benzodiazepines we have tested, l-tryptophan did not impair performance, produce anterograde amnesia, or reduce responsivity during sleep at approximately 2.5, 4, and 6 h post-administration. In our analyses of EEG frequencies, we found that l-tryuptophan administration increased alpha and theta activity in awake subjects but did not alter brain activity in sleeping subjects. We suggested that l-tryptophan acts primarily to modulate arousal level in the awake state, thus setting the stage for more rapid sleep onset. This view is consistent with recent work suggesting that serotonergic systems modulate waking, rather than bring about sleep onset per se. It is important to note, though, that l-tryptophan is a precursor to other substances such as melatonin, so there are alternative pathways which could mediate the l-tryptophan effects.

In operational environments which require continual readiness, l-tryptophan, in doses ranging from 2-4 g, is the agent of choice, since its sleep-promoting effects are readily reversible, and its administration is not associated with an impairment window.

## Introduction

Planning for adequate rest and predicting the consequences of inadequate sleep or cumulative sleep loss should be an important consideration in mission logistics. Provision of food, water, shelter, and equipment have traditionally been the focus of attention while sleep management was ignored. A notable exception to this historical pattern was the concern for the sleep schedule of aircrews in the Falklands conflict. In that encounter, RAF air forces were permitted to use a benzodiazepine hypnotic to help them go to sleep and obtain adequate rest during short rest periods which took place in a safe location, far from the actual point of conflict. The concern for sleep and the acknowledgment of the adverse effects of sleep loss were important factors in the strategic planning of the Falklands effort and established a precedent to be followed by other military planners. In addition, a critical first step was taken by the RAF: there was official recognition of the fact that psychopharmacological aids, in that case the benzodiazepine temazepam, could be used successfully in an operational environment (Baird, Coles, and Nicholson 1983). In a related development, SAC, the Strategic Air Command in the United States, has also officially condoned use of the American formulation of temazepam in specific circumstances. The typical SAC mission involves all-night flying for 12 h or longer, then an opportunity for prolonged daytime sleep, followed by a second nighttime mission, and then a second day of recovery. The SAC flight surgeon initiated an operational test of the effects of temazepam which was conducted by Dr. William Storm of Brooks Air Force Base. In his evaluation, Dr. Storm found that temazepam did promote improved daytime sleep without performance loss 12 h post-administration (Storm and Parke 1986).

In both cases, the sleep medication was taken in a safe environment, in which rest periods were scheduled for known durations and "readiness" was not continuously required. However, in other military operations, there may be a constant requirement that personnel retain the ability to awaken readily at any time post-administration with intact memory and other cognitive and visuomotor skills. We, in our program in research psychopharmacology at the Naval Health Research Center (NHRC), have investigated both "sedating" and "non-sedating" sleeping aids. From our point of view, the term "sedating" sleeping aids has a data-based definition--it is applied to those agents which, in addition to enhancing sleep through some pharmacological mechanism, produce measurable performance decrements and alter responsivity during sleep for some time period post-administration. This time window can be delineated in the research laboratory by repeated sampling of performance and arousal threshold, according to a standard research protocol. Conversely, "non-sedating" agents enhance sleep but do so without producing an "impairment window", as shown by performance and arousal threshold data which are not statistically different from placebo values. Over the years, we have focused on triazolam (Halcion®) as the prototype for the sedating kind of agent (Johnson and Spinweber 1982, 1983, 1984; Johnson, Spinweber, Webb, and Muzet 1985; Spinweber, Johnson, and Webb 1985). We have evaluated the amino acid l-tryptophan as a nonsedating sleeping aid for operational use. In this paper, I will describe the pharmacology of this amino acid, review our studies of its

sleep-enhancing efficacy, and discuss its suitability for military use as a sleeping aid for operational environments.

## Pharmacological Considerations

L-tryptophan is regularly ingested in the diet as a constituent of protein foods. However, the dose of l-tryptophan reported to promote sleepiness or produce sleep-enhancing effects exceeds the amount of l-tryptophan normally eaten in a single meal and equals or exceeds the amount ingested in the normal diet on a given day, that is, 1 to 1.5 g (Cole, Hartmann, and Brigham 1980).

There have been numerous reports that a 1-g dose is effective in reducing sleep latency (Hartmann and Elion 1977; Hartmann and Spinweber 1979; Hartmann, Cravens, and List 1974), but a recent review suggests that larger doses are usually required to promote sleep reliably (Borbely and Youmbi-Balderer 1987). Doses smaller than 1 g are clearly not effective (Hartmann and Spinweber 1979).

An attempt to delineate a dose-response relationship between l-tryptophan in the range 1-15 g and EEG-recorded sleep latency did not show an orderly relationship (Hartmann et al. 1974). There is an indication, though, that loading doses above 3 g saturate the active uptake system so that larger doses produce relatively much smaller increases in the availability of l-tryptophan to brain (Young and Gauthier 1981). While there is no clear dose-response relationship, we have suggested that there may be a smallest effective dose for different populations and different environments (Schneider-Helmert and Spinweber 1986). Hartmann (1981) has reviewed several additional factors which might influence the efficacy of l-tryptophan including subject characteristics (age, severity of insomnia, and pretreatment sleep latency) and time of administration.

It is clear that increasing the dietary levels of l-tryptophan or administering loading doses of l-tryptophan orally do produce increased levels of both total and free l-tryptophan in plasma and that brain levels of serotonin are determined by the availability of the l-tryptophan level in plasma (Moir and Eccleston 1968; Fernstrom and Jacoby 1975; Wurtman and Fernstrom 1976; Young, Hussein, and Murray 1969; Spinweber, Ursin, Hilbert, and Hilderbrand 1983). Administration of l-tryptophan also increases serotonin levels in CSF and produces increases in 5-HIAA (Moir and Eccleston 1968; Eccleston, Ashcroft, Crawford, Stanton, Wood, and McTurk 1970). There is still a question about whether such changes reflect potentiation of activity in central serotonergic systems. There have been reports that activity does not change in median raphe serotonergic pathways (Trulson 1985). L-tryptophan is involved in other metabolic pathways, including metabolism of both tryptamine and melatonin, but most researchers theorize that the sleep-enhancing effects of l-tryptophan are mediated by serotonergic pathways (Young 1986; Oswald, Ashcroft, Berger, Eccleston, Evans, and Thacore 1966; Hartmann, Chung, and Chien 1971; Spinweber et al. 1983). Serotonergic mechanisms were first postulated to control sleep directly by Jouvet (1972). More recent animal data suggest that serotonergic

mechanisms may modulate arousal level in the awake state, rather than potentiating sleep mechanisms per se (Ursin 1976; McGinty and Harper 1976; Trulson and Jacobs 1979; Mouret and Coindet 1980). Koella (1981) has described serotonin as an "anti-arousal" or "dewaking" agent. It is important to note, though, that there have been reports describing hypnotic or sedative properties of melatonin (Cramer, Rudolph, Consbruch, and Kendel 1974; Vollrath, Semm, and Gammel 1975; Lieberman, Waldhauser, Garfield, Lynch, and Wurtman 1984) and there are preliminary data suggesting that it modulates the endogenous circadian oscillator (Arendt, Aldhous, and Marks 1986).

NHRC L-tryptophan Studies

At NHRC, we have conducted three very different studies of the sleep-enhancing properties of the amino acid l-tryptophan. In each study, we tried to enhance sleep in a difficult situation to provide a rigorous test of the effects of the amino acid. In the following sections of this paper, I describe the method and results of each of our three studies. The implications of the three studies when considered together are presented in the Discussion section.

Daytime Nap Study: In the daytime nap study (Spinweber et al. 1983), we wished to determine whether l-tryptophan would enhance sleep during the day at odd and unusual times for sleep. As previously cited, some animal work suggested that serotonergic systems might be involved in the modulation of the waking state rather than sleep induction per se. So, in this daytime study, we also emphasized evaluation of the waking as well as the sleep EEG to identify treatment effects. In addition, numerous metabolic factors, including diurnal rhythms in l-tryptophan availability in plasma, had been identified which suggested that l-tryptophan transfer into brain could be markedly different at various times during the day (Baumann 1985). Cooper (1979), in a review of the effects of l-tryptophan, did agree that the amino acid had sleep-inducing efficacy, but suggested that this property may only exist in the enhancement of nighttime sleep. In our study, 20 normal adults participated. All were employees of NHRC, and all were regular day workers. None reported any significant medical, psychiatric, or sleep problems. The procedure was as follows: Subjects were assigned to either a morning (N = 10) or afternoon (N = 10) nap group. Each subject took two daytime naps, scheduled exactly one week apart. On each occasion, the subject received tablets of l-tryptophan 4 g or matching placebo tablets, assigned in a counterbalanced order. The procedures for the morning and afternoon sessions were identical (Table 1). Seven channels of data were polygraphically recorded: 3 EEG channels, EOGs, EMG, and EKG. Nap records were scored in 30-sec epochs for sleep stages according to the standardized procedures (Rechtschaffen and Kales 1968).

Table 1. Daytime Nap Study Test Schedule.

| Procedure | Morning Group | Afternoon Group |
|---|---|---|
| Subject arrives: apply electrodes | 0830 | 1230 |
| Pre-drug SSS and Thayer | 0845 | 1245 |
| Pill administration (l-tryptophan, 4g, or placebo) | 0850 | 1250 |
| Post-drug SSS and Thayer | 0915 | 1315 |
| Blood Sample Drawn | 0920 | 1320 |
| Waking EEG, eyes open | 0930 | 1330 |
| Waking EEG, eyes closed | 0940 | 1340 |
| Nap period, lights out | 0950 | 1350 |
| Waking EEG, eyes open | 1150 | 1550 |
| Waking EEG, eyes closed | 1155 | 1555 |
| Post-nap SSS and Thayer | 1200 | 1600 |
| Session completed: remove electrodes | 1205 | 1605 |

Two EEG channels ($C_3$--$A_1$+$A_2$, $O_1$--$A_1$+$A_2$) were digitized on-line and the data were stored on magnetic tape for later analysis. The following EEG frequency bands were analyzed: 16-40 c/sec (beta), 13.0-15.5 c/sec (sigma), 8.0-12.5 c/sec (alpha), 4.0-7.5 c/sec (theta) and 0.5-3.5 c/sec (delta). The occipital EEG was used for analysis of alpha activity. All other wave band analyses were performed on the central EEG. Intensity in $\mu V^2$/(c/sec) was obtained by Fourier analysis (Fast Fourier Transform). Time present (sec/min) of alpha and theta was determined by peak-to-peak analysis. The mean frequency for the alpha and theta bands was also obtained.

In this nap study, we found that l-tryptophan significantly reduced daytime sleep latency by about 50% compared to placebo (23.6 min vs. 12.6 min, T (Wilcoxon) = 49, $p<.05$). L-tryptophan was equally effective in the morning and the afternoon administrations. There were no alterations in nap sleep stages. There were changes in alpha and theta activity during waking EEGs: increased alpha time, slowed alpha frequency, and increased alpha intensity, and increased theta time and theta intensity. There were no significant changes in EEG frequency bands during sleep.

Nighttime study: In his review, Hartmann (1981) also identified severity of insomnia as a factor influencing the efficacy of l-tryptophan. In our review paper (Schneider-Helmert and Spinweber 1986), we considered this factor in some detail. Yet, there have actually been few sleep laboratory studies on l-tryptophan which have used well-defined groups of insomniacs as subjects. As part of a comprehensive discussion of insomnia and sleeping pill use, the Institute of Medicine Report (1979) noted that l-tryptophan ". . . has yet to be evaluated for clinical use in various types of insomnia, compared to standard drugs" (p. 34), but that it ". . . appears to shorten sleep latency and promote total sleep . . ." (p. 103). Our nighttime study (Spinweber 1986a) used a well-defined group of chronic, sleep-onset insomniacs as subjects. The protocol was previously employed in a study of triazolam (Halcion®)

(Johnson and Spinweber 1981; Spinweber and Johnson 1982; Muzet, Johnson, and Spinweber 1982). Because previous work on l-tryptophan has suggested that it may act to reduce sleep latency without producing other adverse changes, this protocol included performance, arousal threshold, auditory evoked potentials, and sleep stages as dependent measures.

Subjects were 20 male, sleep-onset insomniacs (mean age 20.3 $\pm$ 2.4 years) who qualified for participation in this study on the basis of both subjective reports about their sleep and on an objective EEG criterion of sleep-onset insomnia, i.e., EEG-recorded sleep latency greater than 30 min.

A parallel, three-phase design was employed (Figure 1).

**12-NIGHT PROTOCOL**

| | | BASELINE | | | TREATMENT | | | | | | WITHDRAWAL | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **NIGHT #** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| **PROCEDURE** | S* | E* | A | C* | E* | A | E* | A | C* | P* | E* | E* |

Figure 1. Protocol for 12-night study. Procedure code: S=screening night; E=all-night EEG for sleep stage scoring; A=auditory arousal thresholds obtained; C=auditory evoked potentials obtained; P=performance batteries administered during awakenings from sleep; *=morning performance testing.

All subjects received placebo during baseline and withdrawal. During treatment, 10 subjects received l-tryptophan 3 g and 10 received matching placebo. Sleep EEGs were recorded on all study nights according to usual procedures. L-tryptophan or placebo was administered at 2115. Lights out occurred at 2200, and subjects were awakened each morning at 0530. Sleep latency was scored for all study nights. Sleep stage data were obtained for statistical comparisons on nights 2, 4, 5, 7, 9, 11, and 12 according to standard procedures (Rechtschaffen and Kales 1968).

Performance and mood test batteries were administered approximately 20-40 min after the morning awakening (approximately 9 h after pill administration). Morning batteries included the NHRC Mood Scale, the Profile of Mood States (POMS), the Card Sorting Test, the Wilkinson 4-Choice Reaction Time Test (performed for 11 min), the Digit Symbol Substitution Test, and the Williams Word Memory Test. On night 10, the performance night, subjects were awakened from Stage 2 sleep during three time

windows (90-100 min, 180-200 min, and 270-300 min after lights out) for mood and performance testing. The average times of performance sessions were 2.5, 4, and 6 h post-pill administration. The threshold for arousal from sleep was obtained on night 3, night 6, and night 8.

A night-by-night plot of mean sleep latency is presented in Figure 2. Between groups t-tests on difference scores showed a significant reduction in mean sleep latency during treatment ($t_{18}$ = 1.81, p<.04, one-tailed). As shown by the within-group tests, sleep latency was significantly reduced in the l-tryptophan group ($t_9$ = 2.08, p<.04, one-tailed) but not altered in the placebo group ($t_9$ = 0.28, n.s.).

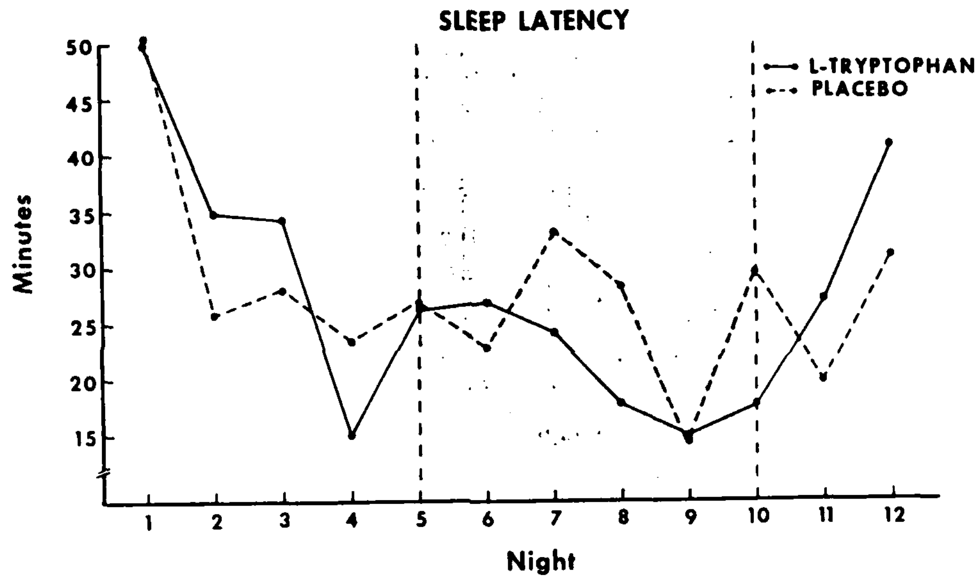


Figure 2. Mean sleep latency for each study night.

Further analysis revealed that sleep latencies were not reduced on the first three nights of treatment, but there was a mean reduction of 16.9 min (49%) in late treatment (nights 8 and 10) compared to placebo-baseline ($t_{18}$ = 2.22, p<.04, two-tailed). This late-appearing effect was confirmed in the within-group test ($t_9$ = 2.35, p<.05, two-tailed). Mean sleep latencies by conditions are presented in Table 2.

Table 2. Nighttime Study Data.

| | L-tryptophan | Placebo |
|---|---|---|
| Condition | $\bar{X}$ ($\pm$SD) | $\bar{X}$ ($\pm$SD) |
| Placebo-baseline[a] (min) | 34.5 (17.8) | 26.9 (11.6) |
| Treatment[b] (min) | 22.5 (8.8) | 28.1 (19.7) |
| Early treatment[c] (min) | 25.7 (11.3) | 27.6 (17.6) |
| Late treatment[d] (min) | 17.7 (7.7) | 28.9 (24.5) |
| Withdrawal[e] (min) | 34.8 (22.9) | 25.3 (9.4) |

[a] Nights 2 and 3.
[b] Nights 5, 6, 7, 8, and 10.
[c] Nights 5, 6, and 7.
[d] Nights 8 and 10.
[e] Nights 11 and 12.

As described in the methods section, the placebo and l-tryptophan groups were statistically compared on many dependent measures. There were no statistically significant differences aside from effects on sleep latency. The two groups did not differ on any other sleep, mood, or performance measure. For the interested reader, more information regarding the other dependent measures, including group means, standard deviations, and F and t-test values, are available in Spinweber (1985).

Field trial: Our third study was unique in that it was the first field trial of the efficacy of l-tryptophan in reducing the sleep-loss component of the jet-lag syndrome (Spinweber 1986b; Spinweber, Webb, and Gillin 1986). Subjects were U. S. Marines stationed at Camp Pendleton, California, who were scheduled for deployment to Okinawa, Japan. Pilot data were collected from 27 Marines (mean age 21.7 $\pm$ 3.2 years). The operational trial was conducted with 51 Marine volunteers (mean age 21.0 $\pm$ 2.2 years). The testing schedule for the operational trial is summarized in Table 3. Baseline data were collected two weeks prior to deployment on three consecutive days (B1, B2, and B3) at 0900 and 1500. On B3, in addition to the 0900 and 1500 batteries, an evening test battery was conducted at 2100. Also on B3, subjects were required to remain awake after the evening test battery until after another battery was conducted at 0300. Two days of preflight data (P1, P2) were collected at 0900 and 1500. During flight, subjective measures and oral temperature were obtained. Arrival at Okinawa was at 1730 local time. An evening test battery was conducted at 2200. Testing on the first two full days (O1 and O2) in Okinawa was at 0900, 1500, and 2100. The study ended at 0800 on the third morning. L-tryptophan 2 g or placebo was administered en route after reboarding at Anchorage and on the first three nights in Okinawa at approximately 2200, following the evening test batteries. To maximize

sleep during flight, environmental interventions included timing of meals and other inflight activities, avoiding caffeinated beverages, and control of cabin lighting.

Table 3. Field Trial Test Schedule.

| Battery | Study Day | San Diego Time | Okinawa Time |
|---|---|---|---|
| 1 | B1[1] | Mon 0900 | |
| 2 | B1 | Mon 1500 | |
| 3 | B2 | Tue 0900 | |
| 4 | B2 | Tue 1500 | |
| 5 | B3 | Wed 0900 | |
| 6 | B3 | Wed 1500 | |
| 7 | B3 | Wed 2100 | |
| 8 | B3 | Thu 0300 | |
| | (two weeks intervening time) | | |
| 9 | P1[2] | Mon 0900 | |
| 10 | P1 | Mon 1500 | |
| 11 | P2 | Tue 0900 | |
| 12 | P2 | Tue 1500 | |
| 13[6] | F[3] | Wed 0900 | |
| 14[6] | F | Wed 1500[5] | |
| 15[6] | F | Wed 2100[5] | |
| 16[7] | F | | Thu 2100[5] |
| 17 | 01[4] | | Fri 0900[5] |
| 18 | 01 | | Fri 1500 |
| 19[7] | 01 | | Fri 2100 |
| 20 | 02 | | Sat 0900 |
| 21 | 02 | | Sat 1500 |
| 22[7] | 02 | | Sat 2100 |
| 23[6] | 03 | | Sun 0800 |

1 "B" indicates baseline days, 2 weeks prior to departure week.
2 "P" indicates days immediately prior to the flight day.
3 "F" indicates day of the flight.
4 "O" indicates days immediately following the day of flight.
5 Battery was delayed due to other requirements (see text).
6 Subjective measures and oral temperature only were obtained.
7 L-tryptophan 2 grams administered at the conclusion of the test battery.

Performance measures included the Wilkinson 4-Choice Reaction Time Test, the Digit Symbol Substitution Test, the Williams Word Memory Test, and the Wilkinson Addition Test. All tests chosen were known to be sensitive to sleep deprivation and to drug effects. Target shooting accuracy was measured 0800 one week prior to departure and on 01. Subjective reports of mood were obtained through use of an Analogue Mood Scale, the POMS, and the Stanford Sleepiness Scale.

Twelve subjects wore Medilog 9-channel recorders for recording of EOG, EEG, skin temperature, EKG, and chest impedance. Medilog subjects wore the devices continuously during waking and during sleep.

L-tryptophan subjects obtained significantly more sleep on the first night in Okinawa compared to placebo subjects (274.5 $\pm$ 19.9 min vs. 222.3 $\pm$ 44.8 min, t = 2.16, $p<.0314$). Total nocturnal sleep time was not enhanced on the following two nights. En route, control of the aircraft environment dramatically increased sleep compared to total sleep time measured in the pilot study. Pilot study Medilog subjects only obtained 120.0 $\pm$ 72 min sleep aboard the aircraft. The range was 16 min of sleep in one subject to a maximum of 3 h 52 min in another. Total sleep time during the operational trial was 291.3 $\pm$ 79.2 min for placebo subjects and 324.3 $\pm$ 145.9 min for l-tryptophan subjects. This 33-min difference in total sleep time between the two groups was not statistically significant. The range of sleep times was 2 to 7 h.

Upon arrival, the l-tryptophan subjects had higher mean self-reported alertness (44.7 $\pm$ 28.1 vs. 31.3 $\pm$ 14.4, $t(47) = 2.09$, $p<.0425$), and a more positive mean rating of overall mood (44.4 $\pm$ 23.2 vs. 31.5 $\pm$ 17.2, $t(47) = 2.20$, $p<.0327$). There were no performance differences between the two treatment groups upon arrival.

Mean reaction time data for the l-tryptophan and placebo groups are presented in Figure 3. L-tryptophan subjects had significantly faster reaction times than placebo subjects at 2100 on 01.

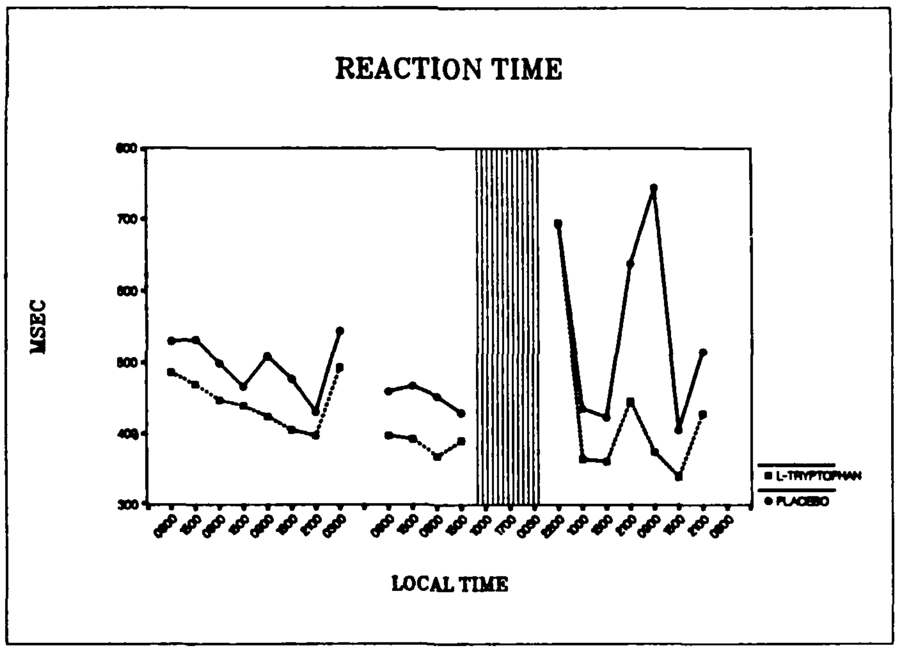


Fig. 3. Mean reaction time on the 4-choice Reaction Time Test for the l-tryptophan and placebo groups separately for all test sessions.

Mean memory data for all performance batteries are presented in Figure 4. The ANOVA showed a significant day-by-treatment group interaction which was due to the fact that, compared to baseline, overall performance in the l-tryptophan group did not decline on O1 and O2, while performance in the placebo group showed a within-group impairment on both days.

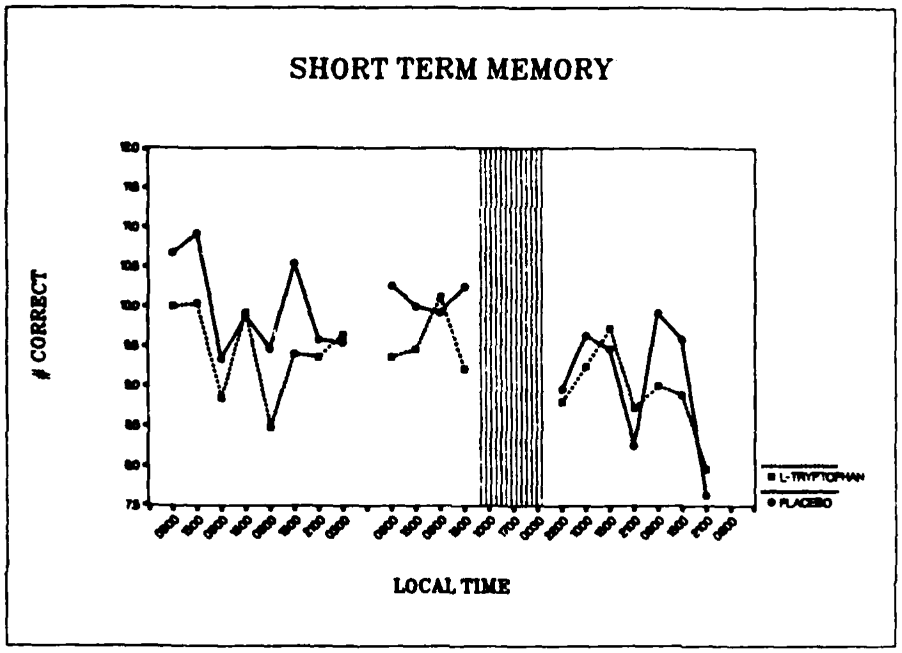


Fig. 4. Mean number correct on the Williams Word Memory Test for the l-tryptophan and placebo groups separately for all test sessions.

As can be seen in Figures 5a and b, in the l-tryptophan group, an evening decrement in memory performance was not present on O1 but did show up on O2. The placebo group curves for O1 and O2 were highly similar to each other, and the evening decrement was present on both days.

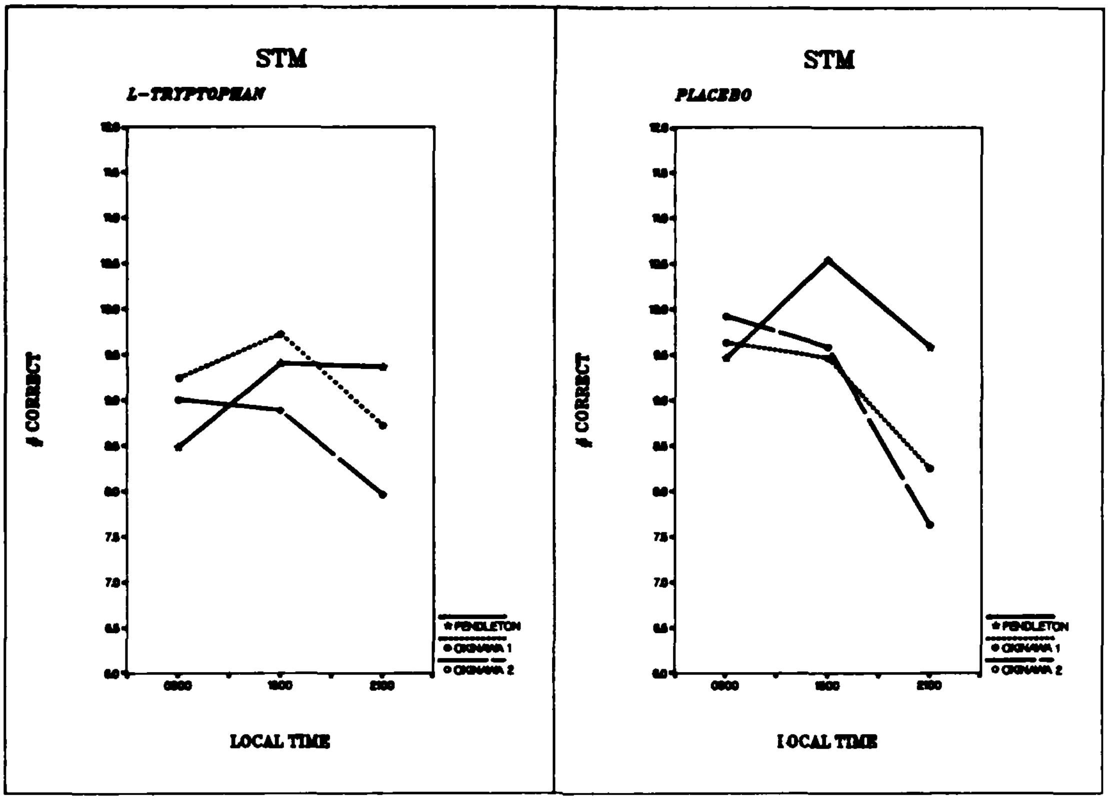


Fig. 5a & b. Mean number correct on the Williams Word Memory Test (STM) at 0900, 1500, and 2100 on study days B3, O1, and O2 for l-tryptophan and placebo groups, separately.

In order to quantify the degree of performance loss occurring in the evenings, the numerical change in mean performance at the time of arrival and on each of the two subsequent evenings was compared to the mean performance obtained during battery 7 (2100 local time at Camp Pendleton). For reaction time, the percentages for the placebo subjects were 61.3%, 48.4%, and 19.9%. For l-tryptophan subjects, the percentage decrements were 72.6%, 12.2%, and 7.7%. For comparison, percentage decrement values were also computed using battery 8 data (0300 at Camp Pendleton) as baseline. For reaction time, for placebo subjects, the percent decrements were 27.4% and 17.3% for the first two nights in Okinawa. Reaction time performance had recovered by the third night. For l-tryptophan subjects, a 39% decrement was present upon arrival, but reaction time performance had recovered after the first night of sleep.

Other performance measures showed jet-lag effects, but there were no treatment-group differences.

## Discussion

In each study, we found that l-tryptophan was effective in promoting sleep. In the daytime study, using normal sleepers, l-tryptophan was effective in reducing sleep latency on the first and only occasion of use. Contrastingly, with chronic insomniacs in the nighttime study, three consecutive nights of use were necessary before effects on sleep latency were evident. These findings are consistent with several other reports (Moldofsky and Lue 1980; Nedopil and Brandl 1980; Brown, Horrom, and Wagman 1979). Any hypotheses regarding the mechanism underlying the late-appearing reduction of sleep latency in chronic, sleep-onset insomniacs could only be speculative at this time. It has been suggested that this effect may be due to the regularization of natural sleep pathways, the induction of enzymes required for biosynthesis, or increased sensitivity of as yet unidentified receptors (Schneider-Helmert 1981; Hartmann, Lindsley, and Spinweber 1983). If some physiological correlate of chronic, sleep-onset insomnia were gradually altered by l-tryptophan administration, it would be reasonable to expect some persistence of the improvement in sleep beyond the period of treatment. A few authors have reported improvements in sleep which did not appear until discontinuation of treatment (Schneider-Helmert 1981; Gnirss, Schneider-Helmert, and Schenker 1978; Hartmann et al. 1983). In our nighttime study, sleep latency returned to placebo-baseline values on the first withdrawal night.

An alternative explanation for the late-appearing effects on sleep latency is a psychophysiological one and is consistent with the point of view previously expressed by Spinweber et al. (1983) that l-tryptophan acts to lower arousal level during waking. It is known that chronic insomniacs have a substantially different psychological "set" regarding sleep which is psychologically and, ultimately, psychophysiologically incompatible with sleep onset. The late-appearing effects of l-tryptophan may be due to repeated experience with the deactivation of the waking state produced by l-tryptophan, which gradually permits the psychophysiological insomniac to learn to relax in bed, thus allowing more rapid sleep onset. Perhaps normal sleepers or mild insomniacs approach bedtime with a lower level of arousal so that the deactivating effects of l-tryptophan are more marked early in administration.

No matter what the mechanism, l-tryptophan was adequately effective to enhance sleep in the field. Aboard the aircraft, even when sleep had been increased dramatically by environmental controls, the l-tryptophan subjects obtained an additional 33 min of sleep en route. For comparison, in laboratory studies of overnight sleep, a mean increase in total sleep time of over 1/2 h compared to placebo would ordinarily be statistically significant and considered to be substantial. There was a statistically significant 52-min increase in total sleep on the first night in Okinawa. There was no sleep-enhancing effect, though, on subsequent nights. It is important to note that most previous studies reporting positive findings on l-tryptophan emphasized effects on sleep latency rather than total sleep time. In fact, in previous studies, when sleep latency was reported to be reduced, total sleep

time was often not statistically increased. In this study in the field, it was impossible to obtain reliable and valid sleep latency measures for individuals, and, therefore, we used total sleep time as a measure of sleep-enhancing efficacy. In view of the use of total sleep time rather than sleep-onset time as the dependent measure of efficacy, we were impressed with both the en route and first-night effect on sleep.

It may be the case that the absence of sleep-enhancing effects on the second two nights in Okinawa was due to inadequate dose size. On the day of the flight, subjects received two doses of 2 g each, one en route and one after the evening test battery. Our previous sleep laboratory study demonstrating daytime sleep-enhancing effects used a 4-g dose (Spinweber et al. 1983). Another factor was the great variability of bedtime on the second and third nights in Okinawa. Although asked to go back to their barracks to go to sleep after the completion of the nighttime performance session, some subjects stayed up much later and some ate at a local restaurant before retiring. I suspect that these behaviors interferred with our assessment of sleep-enhancing effects.

While we found a significant reduction of sleep latency in our nap study, Nicholson and Stone (1979), using the same dose in naps scheduled at 1400, did not find sleep-enhancing effects. The most striking difference between the two protocols was time of administration. In the Nicholson and Stone study, l-tryptophan or placebo was administered at lights out and under both conditions, mean sleep onset occurred less than 23 min later. In our studies, l-tryptophan was ingested at least 45 min before bedtime. Based on our research and other papers, it appears that, while plasma levels change relatively quickly, within 20 min of l-tryptophan administration, subjective effects and effects on sleep latency may not be evident until 45 min post-administration.

Unlike sedative hypnotics, l-tryptophan did not produce impaired performance at any time after administration and did not elevate arousal threshold. The commonly-used sedative hypnotics all produce performance impairment at some dose level for some time after administration (Johnson and Chernik 1982). To my knowledge, the NHRC study (Spinweber 1986a) was the first sleep laboratory study to assess the performance effects of l-tryptophan during awakenings from sleep and in the morning following evening administration. Broadhurst (1977) previously reported that a 2-g dose did not impair reaction time at 2 h after ingestion in a study of awake subjects. Lieberman et al. (1984) found no impairment of performance on simple and choice reaction time tests, on a grooved pegboard test, and on a tapping task 2 h after a larger dose of 100 mg/Kg. Recently, however, Winokur, Lindberg, Lucki, Phillips, and Amsterdam (1986) reported a dose-dependent impairment on symbol copying in subjects who received l-tryptophan 5, 7.5, and 10 g by intravenous infusion. Borbely (personal communication) has raised the question of whether there might be adverse effects on performance early after oral administration--i.e., before 2 h have elapsed. As far as I am aware, while much subjective data has been collected shortly after oral administration (for a review, see Spinweber 1980, 1981), performance data

are not available for that time period. I suspect, though, that performance is not altered soon after administration since there were no early effects on sleep, then, either. In the field, we identified a l-tryptophan-related enhancement of next-day performance on the reaction time test. It is important to note that there have been no laboratory studies of sleeping pills and performance which demonstrated enhanced next-day performance in subjects who take the active pill compared with those taking the placebo. (For an extensive review of such studies and a comprehensive discussion of sleeping pills and performance effects, see Johnson and Chernik 1982.) Our field study was the first demonstration that improving sleep by psychopharmacological means was associated with enhanced performance on any measure of performance the following day.

There is also an indication in the field study data that l-tryptophan administration may have spared memory performance from the effects of jet lag. In addition, reaction time performance recovered more quickly in the l-tryptophan group over the three-day post-flight period. These performance effects may have been due solely to the enhanced total sleep time of the l-tryptophan subjects. It may also be the case that l-tryptophan has separate resynchronizing effects and promotes more rapid adjustment to the new time zone, possibly acting through conversion to melatonin.

## Operational Use of L-tryptophan

L-tryptophan, in doses ranging from 2-4 g, is an effective sleeping aid for use in operational environments. While it enhances sleep, its use is not associated with a "window of impairment." There is no performance loss at operationally-important times post-administration and no alteration in the sleepers' responsiveness to important auditory signals in the environment. Its use does not impair personnel readiness. L-tryptophan may have special usefulness in operations requiring air transport across multiple time zones. It is safe for administration aboard the aircraft and, furthermore, may promote more rapid readjustment to the destination local time.

In planning military missions during which sleep management by psychopharmacological means is indicated, the choice of the kind of pill to use rests primarily upon consideration of the impairment window. If the sleep environment is safe and the duration of the rest period can be established in advance, then a sedating agent, such as a benzodiazepine hypnotic, may be the appropriate choice, since it acts much more rapidly, has more sleep maintenance efficacy, and perhaps acts more consistently than l-tryptophan. (For further discussion, see Spinweber et al. 1983.) However, in other operational environments--aboard aircraft or in dangerous environments--or for use in brief rest periods of undetermined duration, l-tryptophan is the agent of choice, since its sleep-promoting effects are completely reversible and its use is not associated with an impairment window.

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Planning for adequate rest and predicting the consequences of inadequate sleep or cumulative sleep loss should be an important consideration in mission logistics. The use of a sleeping aid may be appropriate to permit personnel to maximize sleep effectiveness in operational environments. At NHRC, we have investigated the amino acid l-tryptophan as a "non sedating" sleeping aid for military use. Attention focused on l-tryptophan because of its role as the dietary precursor of serotonin, the neurotransmitter first identified by Jouvet as involved in the regulation of sleep. Recent reviews continue to debate the effectiveness of l-tryptophan as a sleeping aid and the underlying mechanism for its effects.

At the present time, there seems to be general agreement that l-tryptophan, administered at the right time and in adequate doses, does promote increased sleepiness in awake subjects and more rapid daytime and nighttime sleep onset. In our program in Behavioral Psychopharmacology, we have conducted 3 studies on the efficacy of l-tryptophan using different subject


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Block 19: types and requiring sleep at different times of day or in different environments. In a daytime nap study, normal sleepers were required to take daytime naps at 0950 or 1350, once after l-tryptophan 4 grams and once after placebo. L-tryptophan significantly reduced sleep latency in both morning and afternoon naps. In a study of 6 consecutive nights of use of l-tryptophan 3 grams, young (age 20.3 $\pm$ 2.4 years), chronic sleep-onset insomniacs showed more rapid sleep onset late in administration, but not on the first 3 nights of use. These and other studies suggest that normal sleepers may respond to l-tryptophan administration on the first occasion of use, while more chronic insomniacs may require "pretreatment" before sleep-enhancing effects are evident. More recently, in a study of Marines airlifted to Okinawa, l-tryptophan 2 grams was administered en route aboard the aircraft and 1 hour before bedtime for 3 nights after arrival. Objective sleep data were obtained using Medilog recorders. Total nocturnal sleep was increased by 52 minutes on the first night after arrival. This finding suggests that l-tryptophan is adequately effective to be used in the field to alleviate jet lag. We also evaluated the effects of l-tryptophan on performance, memory, and arousal threshold during sleep using a standard laboratory protocol. Unlike benzodiazepines we have tested, l-tryptophan did not impair performance, produce anterograde amnesia, or reduce responsivity during sleep at approximately 2.5, 4, and 6 hours post-administration. In our analyses of EEG frequencies, we found that l-tryptophan administration increased alpha and theta activity in awake subjects but did not alter brain activity in sleeping subjects. We suggested that l-tryptophan acts primarily to modulate arousal level in the awake state, thus setting the stage for more rapid sleep onset. This view is consistent with recent work suggesting that serotonergic systems modulate waking, rather than bring about sleep onset *per se*. It is important to note, though, that l-tryptophan is a precursor to other substances such as melatonin, so there are alternative pathways which could mediate the l-tryptophan effects.

In operational environments which require continual readiness, l-tryptophan, in doses ranging from 2-4 grams, is the agent of choice, since its sleep-promoting effects are readily reversible and its administration is not associated with an impairment window.

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